IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:	Joan S. Steffan et al.
Serial No.:	10/789,518
Filed:	February 27, 2004
Examiner:	Aditi Dutt
Appeal from Art Unit:	1649
Confirmation No.:	7728
Title:	METHODS AND REAGENTS FOR REDUCING POLYGLUTAMINE TOXICITY
Attorney Docket:	R1:00047

REPLY BRIEF UNDER 37 C.F.R. § 41.41

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Commissioner:

This is a Reply Brief replying to the Examiner's Answer mailed August 5, 2008. Claim 19 remains finally rejected by the Office action mailed July 26, 2007.

(A) Status of Claims

Appellants filed an Appeal Brief on May 21, 2008 seeking reconsideration of the sole remaining pending claim, which was objected to and finally rejected in an Office action dated July 26, 2007. The Examiner responded to the Appeal Brief with an Examiner's Answer mailed August 5, 2008, which withdrew the objections but maintained the rejection of claim 19. Therefore, Appellant submits that the claims listed in the Amendment dated March 5, 2007 is still the appropriate subject matter of this appeal.

(B) Grounds of Rejection to be Reviewed on Appeal

The sole ground of rejection remaining to be reviewed on appeal is the rejection of claim 19 under 35 U.S.C. §112¶1 as failing to comply with the enablement requirement.

(C) Argument

Response to Rejection Under 35 U.S.C. § 112, First Paragraph

(1) Reply to Section 9, Paragraph 5 of Examiner's Answer

Appellant will focus this reply on the sole rejection that remains at issue in this case, namely, the Examiner's rejection of the sole remaining claim (19) under 35 USC §112, first paragraph, for lack of enablement. Specifically, the Examiner states,

> The specification does not reasonably provide enablement for treating Huntington's disease (HD), in a patient diagnosed with HD, comprising administering a therapeutically effective, SUMO isopeptidase enhancer. (Examiner's Answer, page 4, paragraph 2.)

The Examiner goes on to set out the factors used to evaluate Appellant's disclosure, including the nature of the invention, the state of the prior art, the predictability of the art, the amount of guidance present, the presence of working examples, the breadth of the claims, and the quantity of experimentation needed to carry out the invention. (Examiner's Answer, page 4, paragraph 3.) In turn, the Examiner characterizes the state of the prior art and Appellant's own disclosure on pages 5 to 7 of the Answer. Appellant strongly disagrees with the Examiner's characterization of Appellant's disclosure, as well as the state of the prior art.

First, on page 5, paragraph 5, the Examiner sets forth his understanding of Appellant's disclosure, stating in relevant part:

- The specification of the instant application teaches that long repeats of polyglutamine (polyQ) results in neurodegenerative diseases, for example Huntington's Disease (HD);
- The specification teaches that a truncated portion of the mutant Huntingtin protein Httex1- causes Huntington's disease like disorder in mice and flies; and
- SUMO-1 modifies protein function.

Appellant believes the Examiner at best minimizes, and in some cases mischaracterizes, the actual teachings set forth in the specification, particularly as the Examiner's entire analysis focuses on the Background of the Invention and exactly one page (page 12) of the extensive Detailed Description provided. Appellant would suggest that a thorough review of the disclosure provided in the specification shows that what is provided is nothing less than the identification of one of the *principal* mechanisms in the development of Huntington's Disease, and the subsequent discovery of a method to prevent the operation of this mechanism. For example, Appellant discloses,

- The portion of the Huntingtin protein implicated in the SUMO mechanism, and more specifically that the first 17 amino acids of the Huntingtin protein are modified by SUMO-1. (See, Fig. 1; page 8, lines 4 to 37; and page 20, line 35 to page 21, line 24.)
- Appellant then goes on to address how this critical portion of the Huntingtin protein is impacted by SUMOylation, demonstrating that SUMO modification of Huntingtin increases the production of toxic oligomers that are part of the pathogenic process in HD. (See, Fig. 2a; page 9, lines 1 to 34; and page 21, line 24 to page23, line 26.)
- Appellant also demonstrates that SUMO-1 also plays a role in transcriptional repression, which is a well-known part of the HD pathogenic process. (See, Fig. 2b; and page 23, line 27 to page 24, line 28.)
- Appellant further demonstrates that even "chronic low level" SUMOylation would contribute to progressive HD pathology. (See, Fig. 2c ; and page 24, line 29 to page 25, line 22.)
- Finally, after determining the portion of the Huntingtin protein impacted by SUMO and also by demonstrating that SUMO has multiple

> negative impacts on the pathology of HD, Appellant then demonstrates that the reduction of SUMO activity reduces neurodegeneration and improves neuropathology, and that blocking SUMOylation is the dominant method for improving the pathology. (See, e.g., Figs. 3 to 5; page 10, line 22 to page 11, line 30; and page 27, line 22 to page 29, line 9.)

On this last point Appellant writes in relevant part,

> These observations demonstrate that Htt can be SUMOylated and suggest that SUMOylation can increase Htt accumulation, decrease aggregate formation and possibly increase toxic oligomers, potentially mask a cytoplasmic retention signal and increase nuclear repression of transcription. The impact of SUMOylation on HD pathogenesis *in vivo* is dramatic.
> (Specification, page 28, lines 30 to 36.)

Moreover, Appellant highlights the nature of their discovery such that one of ordinary skill in the art could not possibly miss the import, stating,

> The present inventors have provided a clear demonstration of reduced polyglutamine toxicity in response to a loss in the ability of *Drosophila* cells to SUMOylate proteins *in vivo*. It is proposed that a reduction in the SUMOylation of pathogenic mutant polyglutamine repeat protein causes it to become unstable and to be degraded much more quickly than when it is SUMOylated. Therefore, drugs designed to block SUMOylation of mutant polyglutamine repeat proteins, or drugs designed to enhance removal of SUMO-1 from these proteins, should have a therapeutic effect in the treatment of HD and other polyglutamine-repeat diseases.

(Specification, page 14, lines 15 to 27.)

The Examiner appears to disregard or ignore this extensive discussion and the related data results, instead focusing solely on the *Drosophila* fly study and the general background discussion provided in the initial section of the specification. Moreover, the Examiner rebuts the results of Appellant's very detailed scientific studies with generic statements that HD is difficult to treat and that SUMO is a part of a complicated "network of modifying and demodifying enzymes", without, seemingly, to consider any of the data described above. (Answer, page 10, paragraph 12.) Accordingly, it is Appellant's position that when the disclosure provided in the specification is considered as a whole it becomes clear that the single remaining claim is fully enabled.

(2) Reply to Section 10, Paragraphs 10 to 17 of Examiner's Answer

The Examiner makes six arguments concerning the suitability of Appellant's disclosure with regard to the use of SUMO isopeptidase enhancers to treat HD. These arguments will be addressed in the sections below.

(i) Reply to Section 10, Paragraph 12 of Examiner's Answer

First, the Examiner argues that there are as many as 50 SUMO targets and so, presumably, that it would not be clear to one of skill in the art as to which SUMO target would be important or efficacious at treating HD. This is an argument that would have merit were it not for Appellant's detailed investigation and discussion of the specific SUMO target that would be of interest in treating HD. Indeed, the first four data graphs presented by Appellant, and the subsequent discussion of each, are entirely focused on identifying the protein implicated in HD, and even more specifically which portion of that protein is impacted by SUMOylation. (See, e.g., Specification, page 8, lines 4 to page 10,

line 21; page 12, lines 17 to 35; and page 19, line 31 to page 27, line 21.) For example, in the very section of the specification cited by the Examiner the Appellant writes,

> Httex1p was found to be SUMO-1 modified and ubiquitinated. Mutation of three lysine residues in the amino-terminal 17 amino acids of expanded Httex1p to arginine (K6R, K9R, and K15R) reduces stability of this polypeptide in cell culture. In mutagenesis studies, lysines 6, 9, and 15 were found to be important for SUMOylation of Httex1p and ubiquitin and SUMO-1 may compete for lysines 6 and 9.
> (Specification, page 12, lines 27 to 35.)

In short, one of ordinary skill in the art is not given a blank slate by Appellant upon which he must determine the essential SUMO target for addressing HD. Rather, Appellant provides not only the gene and protein in question, but also the location on that protein implicated by SUMOylation. As such the Examiner's central thesis, namely, that one of skill in the art would have a vast and uncertain array of potential SUMOylation targets to choose from ignores a substantial portion of Appellant's specification. Accordingly, even though Melchior, et al. do indicate that SUMO proteins are "reversibly coupled to numerous intracellular targets", a review of Table 2 cited by the Examiner for support of this argument shows that most are irrelevant to HD and would be ignored by one of ordinary skill in the art after having read Appellant's disclosure. (Melchior, et al., Abstract & Table 2.)

Moreover, even were such a person to ignore all the teachings provided by Appellant, by the Examiner's own admission they would only be required to examine some 50 species, which Appellant submits is simply not undue given the level of skill in the art and today's analytical techniques. Indeed, on this last point it should be noted that the Examiner acknowledges that the *Drosophila* fly model taught by the current

application itself "provides a cost-effective platform for testing large matrices of drug combinations." (Answer, page 18, paragraph 20.) As such, even were one of ordinary skill in the art to find it necessary to test the fifty odd SUMO isopeptidases cited by the Examiner, Appellant's specification discloses exactly how to carry out those experiments in a cost-effective manner, and without undue experimentation. (See, e.g., Specification, page 17, line 20 to page 18, line 12; and page 29, lines 10 to 37.) Accordingly, Appellant finds it contradictory for the Examiner to make such an admission and simultaneously argue that the "state of the art" at the time would have required undue experimentation to identify a candidate drug from such a limited number of candidate compounds.

(ii.) Reply to Section 10, Paragraph 13 of Examiner's Answer

The Examiner's second point is really nothing more than a duplication of the previous "number" argument, this time directed to the actual target of Appellant's claims, namely, SUMO isopeptidase enhancers. Appellant will repeat the points made above, specifically, that were the current specification silent as to the nature of the target gene or the SUMOylation process then the Examiner's argument might have some validity. In the application at issue this is simply not the case. Appellant has specified with detail the target genes/proteins as well as the SUMOylation interactions that are of interest in the pathology of HD. (See, e.g., discussion of Figures 1 to 4.)

Accordingly, it is simply not true that one of skill in the art would be without guidance on the SUMO isopeptidases that could be effectively enhanced to treat HD. In addition again, even were such an argument to be true, Appellant specifically teaches a technique the Examiner acknowledges provides an effective screening method for large numbers of potential treatments, and there are simply not a sufficiently large number

of potential target compounds that testing each one for efficacy would amount to "undue" experimentation.

(iii.) Reply to Section 10, Paragraph 14 of Examiner's Answer

The Examiner's third point is that one of skill in the art would not have been able to extrapolate from the *Drosophila* test results that enhancing SUMO isopeptidase would work to reduce the pathogenesis of HD. This argument would seem to ignore the consistent teachings of the literature, both cited in the specification and by the Examiner in his Office action, that one of the principal features of ubiquitin-related molecules, including SUMO proteins, is that they are reversible by "deubiquitinating enzymes (isopeptidases)." (Melchior, et al., *Annu. Rev. Cell. Dec. Biol.* 16: 591-626, 2000, page 592, 1st paragraph)

For example, Melchior, et al. write, "like ubiquitination, SUMO modification is reversible." (Melchior et al., *Annu. Rev. Cell. Dec. Biol.* 16: 591-626, 2000, page 597, 1st paragraph.) The authors then go on to recite that four SUMO C-terminal isopeptidases had been identified at the time of the article. Accordingly, it is simply not true that there is substantial disconnect between Appellant's finding that lower SUMOylation rates improve HD pathogenesis, and Appellant's claim that SUMOylation levels should be controlled by controlling levels of SUMO isopeptidase. Indeed, as the prior art and Appellant's own specification indicate, the action of these molecules is a well-known and well-studied feature of ubiquitin-related proteins.

(iv.) Reply to Section 10, Paragraph 15 of Examiner's Answer

The Examiner's fourth point is really a summary of the previous three points, namely, that given the state of the art in SUMO isopeptidase , the complexities of HD, the lack of available treatments at the time, insufficient guidance from the specification,

and no knowledge about the isopeptidase enhancers, that a leap from a fly model to humans would require undue experimentation. Obviously, Appellant disagrees strongly with the Examiner's characterization of the record in the current application.

As discussed above, even in 2000 when the Melchior et al. publication was written the function of SUMO isopeptidase was well-known and understood. Appellant's own disclosure addresses many of the complexities of HD, including providing information about the function of SUMOylation as it pertains to HD. Appellant also rejects the Examiner's assertion that the specification provides no guidance to one of skill in the art. Indeed, Appellant again would point out that any thorough review of the specification, and particularly the discussion of the experimental results related to FIGs. 1 to 4 which are ignored in the Examiner's analysis of this application, shows that the disclosure provides a great deal of information on both the structure and function of SUMO in the pathogenesis of HD and how it can be used to effectuate a treatment. A discussion of the Examiner's final assertion, that the fly model represents an "unpredictable" leap, will be discussed in the next section of this brief.

(v.) Reply to Section 10, Paragraph 16 of Examiner's Answer

The Examiner's fifth point is that "there is no evidence or sound scientific reasoning presented in the case, that administration of a SUMO isopeptidase enhancer would be beneficial to treat HD in a patient." (Answer, page 13, paragraph 16.) The Examiner then goes on to restate the initial argument made in this section of the Answer, namely, that "one skilled in the art would not be able to predict from the instant specification or the state of the prior and post art, that enhancers to all possible SUMO isopeptidases will be therapeutically effective in treating HD." (Answer, page 14, paragraph 16.)

Although these arguments are for the most part duplicative of the arguments made by the Examiner in paragraphs 12 to 14, Appellant would merely like to reemphasize that the Examiner's argument would seem to require one to ignore the vast bulk of Appellant's disclosure. Specifically, the application details the portion of the HD gene impacted by SUMO, it details the function of SUMO as it applies to the pathogenesis of HD, and it details how reducing SUMOylation can improve that pathogenesis. Finally, it is simply not true to say that Appellant never provides any "sound scientific reasoning" as to why administration of a SUMO isopeptidase enhancer would be beneficial to treat HD in a patient. For example, Appellant writes,

> The present inventors have provided a clear demonstration of reduced polyglutamine toxicity in response to a loss in the ability of *Drosophila* cells to sumoylate proteins *in vivo*. It is proposed that a reduction in the SUMOylation of pathogenic mutant polyglutamine repeat protein causes it to become unstable and to be degraded much more quickly that when it is SUMOylated. Therefore, drugs designed to block SUMOylation of mutant polyglutamine repeat proteins, or drugs designed to enhance the removal of SUMO-1 from these proteins, should have a therapeutic effect in the treatment of HD and other polyglutamine-repeat diseases.
>
> The consequence of polyglutamine repeat disease is slow and wasting death with no treatment options available. Any option to slow or prevent the process would be desirable. The invention has clear public and commercial use in the treatment of HD and other polyglutamine repeat diseases and potentially as well in neurodegenerative and psychiatric diseases in general.
>
> (Specification, page 14, lines 15 to 35.)

Moreover, this is merely the conclusion of what Appellant considers to be a very "sound" and well-reasoned section of the disclosure that explains exactly how and why the current invention works. (See, Specification, page 12, line 17 to page 14, line 35.) In short, Appellant disputes the Examiner's seemingly out-of-hand dismissal of dozens of pages of the specification as apparently irrelevant to the instant invention and lacking in substance. Appellant would submit that the disclosure provides a detailed roadmap on how SUMO interacts with the HD gene and impacts the pathogenesis of HD, how the reduction of SUMOylation improves the pathogenesis of HD, and as reflected in the passage above, that SUMO isopeptidase enhancers are a good method of effecting a reduction in SUMOylation. Moreover, as acknowledged by the Examiner, Appellant also provides a disclosure of how to efficiently screen for effective treatment compounds such that even were some review of multiple species required, it would not require "undue" experimentation.

(vi.) Reply to Section 10, Paragraph 17 of Examiner's Answer

In conclusion, Appellant strongly disagrees with the Examiner's characterization, and really minimization, of the scope of the disclosure provided by the specification of the invention. The specification provides scientific studies that detail the mechanism of SUMOylation in the pathogenesis of HD and how reducing SUMOylation can improve the pathogenesis of HD. In addition, both Appellant's disclosure and the art cited by the Examiner teach the well-know reversibility of SUMO using SUMO isopeptidases. Finally, Appellant provides a method for screening therapeutics that the Examiner acknowledges is effective and efficient, thereby contradicting the Examiner's own argument that the experimentation required to determine an effective SUMO isopeptidase enhancer would be undue.

(3) Reply to Section 10, Paragraphs 18 to 28 of Examiner's Answer

Ostensibly this section of the Examiner's Answer is focused on addressing Appellant's extended argument concerning the correlative nature of the *Drosophila* fly model used to show that reducing SUMOylation could improve the pathogenesis of the fly. However, a review of the arguments made by the Examiner show that the question of the fly model has receded in importance, and many of the arguments in the paragraphs that follow duplicate the ones addressed earlier in this brief

(i.) Reply to Section 10, Paragraph 19 of Examiner's Answer

The Examiner central thrust in this section is that the fly model results do not represent a "working example" because they do not show the effect of directly administering a deSUMOylation enhancer. The Examiner also repeats the earlier argument that "the state of the art with respect to SUMO isopeptidase and enhancers thereof is premature" and that "the molecular processes of pathogenesis of Huntington's disease are yet to be fully uncovered." (Answer, page 17, paragraph 19.) Again, as explained in detail in the previous section, the Examiner's arguments only have merit if one of skill in the art were to ignore all the other data and disclosure provided in prior art and in Appellant's specification. Specifically, the Melchior et al. reference and Appellant's own specification make it clear that the function of SUMO isopeptidases as mechanisms to reverse SUMOylation are and have been well-known for some time. (See, e.g., Melchior et al., *Annu. Rev. Cell. Dec. Biol.* 16: 591-626, 2000, page 597, 1st paragraph; Muller, et al., *Nature* 2: 202-210, 2001, page 203, col. 2, 2nd paragraph; and Melchior, et al., *TRENDS in Biochem. Sci.* 28:11 612-618, 2003, page 612, col. 1, paragraph 1 & 2.)

In short, while each of these references raises questions about the overall mechanism of SUMOylation, all of them agree that the isopeptide bond is the location of the covalent interaction between SUMO and its target, and that in turn the introduction

of SUMO isopeptidase results in deSUMOylation. However, the Examiner focuses the attention of this inquiry on peripheral debates about the overall structure and function of SUMO in the larger biochemical context. Similarly, Appellant's disclosure provides numerous experimental results (see discussion of FIGs. 1 to 4) concerning the effect of SUMO on the molecular process of HD. Again, rather than focus this inquiry on the validity of those results the Examiner dismisses them and instead cites to Feigin, et al. and argues broadly that HD is "complex" and that the full mechanism of the disease is not known. (Answer, page 17, paragraph 19.)

Appellant does not profess to have mapped out the full function of SUMO, nor the full pathology of HD. Appellant instead has shown, by rigorous scientific experiment and without dispute from the Examiner, that the pathogenesis of HD is ameliorated by reducing the SUMOylation of the Huntingtin protein. Appellant does not suggest that the treatment proposed by the current invention is the *only* or even the best answer to treating HD. Instead, Appellant merely suggests that the current treatment regime provides an option for at least slowing the pathology of HD, stating,

> The consequence of polyglutamine repeat disease is slow and wasting death with no treatment options available. Any option to slow or prevent the process would be desirable.
> (Specification, page 14, lines 28 to 30.)

The Examiner's continued attack on the enablement of the current application seems to hold Appellant to an unduly burdensome standard, namely, that Appellant know not only that the current method works, but also exactly how and why the current method works in relation to all of the other molecular processes of HD. This is not the appropriate standard of review. Quoting the MPEP regarding the *In re Wands* case,

> In In re Wands, the Court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known."
>
> (MPEP, §2164.01(a), citing *In re Wands*, 858 F.2d at 740, 8 USPQ2d at 1406.)

In the current application, and in the relevant prior art at the time ,there is and was considerable direction and guidance as to how SUMO effects the pathogenesis of HD, how reducing SUMOylation improves this pathogenesis, and how to screen for compounds that would be acceptable for use in reducing the SUMOylation. In addition, there can be no dispute that there is and was at the time the application was filed an inordinately high level of skill in the biotechnical arts. Finally, all of the methods needed to practice the invention were either disclosed explicitly in the application or were well-known at the time the application was filed. Accordingly, Appellant does not understand how practicing the current invention would entail "undue experimentation", as alleged by the Examiner.

(ii.) Reply to Section 10, Paragraphs 20 to 25 of Examiner's Answer

These sections again raise the issue that, in the last Office action, was the focus of the Examiner's rejection, namely, that "to test for treatment of a disease in a subject, one would need to conduct studies on non-human mammals." (Answer, page 18, paragraph 20.) The Examiner argues first that under the law, and by general consensus, mammalian models are a "prerequisite" to human trials. (Answer, page 18, paragraph 20, citing Wang et al.) The Examiner then asserts that the *Drosophila* fly model is "more important as a pre-screen for testing and identifying drugs for treatment." (Answer, page 19, paragraph 21.) The Examiner also argues, without

support save the general statement in the Feigin et al. reference that animal trials need to be "viewed with caution", that one of skill in the art would not "be able to extrapolate results from the fly to a human". (Answer, page 20, paragraph 22, citing Feigin et al. *Curr. Opin. Neurol.* 15: 483-489, 2002.) The Examiner further argues, bizarrely, that Wang et al. cites *Drosophila* models as useful principally for high-throughput screening despite the article's clear statement, echoed in the Examiner's Answer, that, "by *every* measure flies expressing mutant human genes present with pathology that mimics the human disease in *every* important way." (Answer, page 20, paragraph 23, citing Wang et al., emphasis added.)

Appellant does not believe anything provided in these portions of the Examiner's Answer address the central thrust of Appellant's initial Appeal Brief, or even the Office Action Response filed April 10, 2007. Wading through the arguments from the Examiner the central tenet seems to be that the fly model is *better* used for high-throughput screening, that animal models are *required* by law prior to initiating human testing, and the one author (Feigin et al.) has suggested using caution in relying on animal studies for HD. None of these points at all address the central legal test at issue, that of correlation. Specifically, according to case law it is not Appellant's job to prove that the test method used is the *best* or provides absolute certainty, it is only required that "one skilled in the art would accept the model as reasonably correlating to the condition." (MPEP §2164.02).

In the instant application, while the fly model might be better suited for high-throughput screening that does not mean that the actual screening performed is not also efficacious. Indeed, Appellant would draw the Board's attention once again to pages 8 to 12 of the Office Action Response filed April 10, 2007. This portion of that previously filed response provides numerous and repeated examples of the efficacy of both the *Drosophila* model used in this invention and other *Drosophila* models. This

section also shows that these models are thought by those of skill in the art to "reasonably correlate" to the diseases they model.

Further, while the Examiner repeatedly argues that legally mammalian models would be required before proceeding to human test subjects, this is simply not a legitimate basis for determining enablement. To require an Appellant to meet the standard set forth by the FDA would create a *de facto* requirement that every invention dealing with human disease treatment be fully reduced to practice.

Finally, Appellant is truly puzzled by the Examiner's continued citation to Wang et al. The Wang et al. article provides a number of statements that fully support Appellant's use of the fly model. For example, Wang et al. write,

- The fly is one of the best invertebrates for modeling higher organisms.
- The fly is also an excellent choice for modeling neurodegenerative diseases because it contains a fully functional nervous system with an architecture that separates specialized functions such as vision, olfaction, learning and memory.
- Thus, by every measure, flies expressing mutant human genes present with pathology that mimics human disease in every important way.

(Wang et al., page 1294, col. 2, last paragraph to page 1295, col. 1, 2nd paragraph.)

Even the section of the article cited by the Examiner as indicating a weakness in the model says nothing about the efficacy of the fly to model human disease, rather it seems to Appellant that Wang et al. are discussing how to make the model *more* amenable to high-throughput and automated screening. The full quote states,

> How to make *Drosophila* models more amenable to high-throughput and automated screening for therapeutics is an important issue. In this regard, practical hurdles to be overcome are the automated manipulation and scoring of flies and the fact that flies are not accessible to externally administered drugs.
> (Wang et al., page 1295, col. 1, 2nd paragraph.)

In short, none of the references cited ever raise any question as to the ability of fly models to model HD. In fact, the references cited seem to universally regard the fly model as excellent in its ability to "correlate" to human disease, specifically neurodegenerative disease, and even more specifically HD. Accordingly, Appellant again respectfully submits that under the appropriate legal standard the fly model used in the application should be considered a "working example".

(4) Conclusion

In conclusion, Appellant believes that a proper application of the Wands factors has not been done, or at least that the application of the factors is incomplete in its failure to consider the full scope of the teachings presented in Appellant's specification.

- First, Appellant provides substantial guidance as to the relevant portion of SUMO implicated in HD, how SUMOylation impacts the pathogenesis of HD, and how reduction of SUMOylation ameliorates HD pathogenesis.

- Second, Appellant does provide a working example that shows improvement in the pathogenesis of HD when the level of SUMOylation is reduced. The prior art and Appellant also provide numerous teachings that show that one of skill in the art would have been well aware that enhancing levels of SUMO isopeptidase would be a very facile way of affecting such a reduction.

- Third, the working example uses a fly model that both current and contemporaneous art indicates "mimics human disease in every important way."

- Fourth, the complex nature of the invention is reduced because Appellant provides extensive testing data showing exactly how SUMO influences the pathogenesis of HD, and how its reduction ameliorates this pathogenesis. The complexity of the disease is also mitigated by the extremely high level of skill found in the art.

- Finally, even if necessary, the level of experimentation required to screen all possible SUMO isopeptidases (approximately 50 according to the Examiner) would not be undue when one considers the state of the art, the screening technologies available, and the fact that Appellant's own application discloses a screening method in the fly model that the Examiner acknowledges is efficient and cost-effective.

(4) Conclusion

Based on these factors, Appellant would submit that the sole remaining claim of the invention is fully enabled by Appellant's disclosure and respectfully requests that the Examiner's rejection be set aside.

Respectfully Submitted,

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